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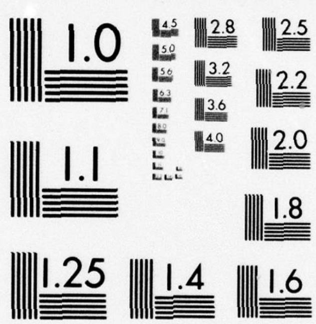

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TECHNICAL REPORT NO. 127

ESCHERICHIA COLI SHOCK IN THE BABOON AND THE RESPONSE TO ADRENOCORTICOSTEROID TREATMENT

L. B. Hinshaw, J. J. Coalson, B. A. Benjamin, L. T. Archer,

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University of Oklahoma Health Sciences Center
Departments of Physiology & Biophysics, Pathology,
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The incidence of septic shock has increased significantly in the United States with the occurrence of over 100,000 deaths per year according to McCabe (27). Much effort has been directed toward the development of experimental animal models more closely resembling the clinical situation. The dog administered live Escherichia coli organisms has proven to be a useful shock model, as reported by Archer (1) and Griffiths (11), Groves (12) and Hinshaw (15) and their colleagues. Recently, however, emphasis has been placed on the nonhuman primate as an experimental septic shock model. Coalson (6), Cryer (10), Herman (13), Hinshaw (17,19) and Horwitz (22) and their co-workers have been instrumental in developing experimental procedures with baboons receiving lethal intravenous administrations of live Escherichia coli organisms. Results have demonstrated marked hemodynamic, respiratory, metabolic, hematologic and morphologic abnormalities bearing distinct resemblances to the human entity of septic shock. Attempts to treat this latter model, however, have been uniformly unsuccessful in terms of preventing the lethal endpoint of shock.

Corticosteroid administration in endotoxic, live Escherichia coli, or septic shock has yielded conflicting results. The studies of Herman (13) and Pingleton (29) and associates have been negative, whereas benefits have been shown by Schumer (35) and Hinshaw (14,16), Holtzman (21), Latour (24), Pitcairn (30), Rao (32), Sambhi (33), Schuler (34), Vaughn (37) and White (38) and their co-workers. Improvements in cardiac output, regional blood flow and metabolism, prevention of generalized intravascular clotting, and increased survival rate in these studies have been demonstrated by treatment with large doses of adrenocorticosteroids.

The purpose of the present study is two-fold; first, the response of the awake baboon to a slow infusion of Escherichia coli organisms will be examined

in order to evaluate its effectiveness as a model in approximating the condition of the human patient. Second, the effectiveness of the corticosteroid, methylprednisolone sodium succinate, administered alone as a treatment for septic shock in the unanesthetized baboon, will be evaluated with respect to various hemodynamic, metabolic and hematologic parameters, tissue morphology and survival.

METHODS

Experiments were carried out on 12 healthy baboons, *Papio anubis*, weighing between 9.6 and 19.1 kg. Animals were fasted overnight and given water *ad libitum*. The following morning they were restrained with a squeeze cage device and administered ketamine hydrochloride (Ketaset; Bristol Laboratories, Syracuse, N.Y.), 14±0.5 mg/kg intramuscularly. Femoral vessels were exposed and cannulated in one hind limb for pressure measurements, fluid, live organism and steroid administration, and blood sampling. Animals were positioned comfortably in a primate restraining chair, inclined at 45°, and a Tele-Thermometer probe was inserted in the rectum. A 3-hour equilibration period post-ketamine was allowed to insure that animals were awake, had reached a steady state, and exhibited a quiet behavior. During the period of equilibration, saline was infused intravenously at the rate of 3 ml/kg/hour to satisfy minimum body fluid requirements, but infusions were decreased if the hematocrit fell excessively.

Mean arterial pressure and heart rate were monitored on a Sanborn recorder. Arterial blood samples were taken for control determinations of plasma glucose, serum insulin, hematocrit (Hct), leukocyte concentration, differential leukocyte concentrations, pH, lactate, sodium (Na^+), potassium (K^+), serum cortisol, serum glutamic pyruvic transaminase (SGPT) and arginase. Glucose, pH, Hct,

and leukocyte concentrations were recorded hourly while other parameters were collected at predetermined intervals.

Animals were paired in each group by infusing comparable intravenous doses of Escherichia coli organisms prepared as previously reported (18,19) and administered during a 5-hour period with one member of each pair receiving methylprednisolone sodium succinate (MP) (Solu-Medrol; The Upjohn Company, Kalamazoo, Mich.). Three groups were studied and mean Escherichia coli doses were as follows: Group A (N=4), 2.9×10^{10}; Group B (N=2), 1.9×10^{10}; and Group C (N=5), 5.6×10^{10} organisms/kg. Animals in Group B were administered one intramuscular dose of gentamicin sulfate (Garamycin; Schering Pharmaceutical Corp., Kenilworth, N.J.), 4.4 mg/kg, at 1.5 hours after the total Escherichia coli dose was administered. One additional baboon was administered saline in place of organisms and continuously observed for a 24-hour period. A summary of the Escherichia coli doses infused and therapy instituted is shown in Table I. Animals were continuously observed for a 24-hour period or until death. Tissues were removed for evaluation following nembutal administration from survivors at the 24th hour and from nonsurvivors when mean blood pressures fell to 25 mmHg, in order to eliminate tissue damage due solely to hypoxia. Specimens of heart, liver, kidney, adrenal, lung, intestine, skin and pancreas were obtained for morphologic evaluations and are the subject of a separate report (7).

Plasma glucose was determined by a glucose analyzer with an accuracy of ±3 mg%, serum insulin was obtained by radioimmunoassay and pH was determined by a blood gas analyzer, as previously reported (18,19). Total leukocyte concentrations were measured with an automatic particle counter (Coulter Z_F; Hialeah, Florida) and differential leukocyte concentrations by microscopic examination of blood smears stained with Wright's stain. Arginase concen-

trations were determined using "Chem assay" kits (Pitman-Moore, Inc.; Washington Crossing, N.J.) and SGPT levels were measured using a Serosonic test kit (Mallinckrodt, Inc.; St. Louis, Mo.). Sodium and potassium concentrations were determined with an Instrumentation Laboratories Model 143 Flame Photometer. Cortisol concentrations were measured by radioimmunoassay (23) and lactate concentrations were determined with perchloric acid, glycine-hydrazine buffer, NAD^+ and lactic dehydrogenase.

Baboons given MP received bolus injections of 30 mg/kg at 15 minutes after initiation of Escherichia coli infusion and subsequent 2-hour infusions of 15 mg/kg at 2-hour intervals. The initial MP bolus injection, given at 15 minutes, was considered essential since by that time a large number of organisms had been infused (2.0×10^9 organisms/kg body weight). Maintenance infusions were considered essential because of the short half-life of MP, determined to be 3-4 hours by DiSanto (The Upjohn Company; Kalamazoo, Mich.).

RESULTS

Figures 1A, 1B, 1C and 1D illustrate the responses of four baboons given a mean dose of 2.9×10^{10} live Escherichia coli organisms per kg (designated as low dose--Group A). Animals 1 and 2, 5 and 6 are paired and all are given comparable doses of Escherichia coli organisms with baboons 2 and 6 being administered methylprednisolone (MP). Figure 1A shows that mean systemic arterial pressure (MSAP) responses are variable with baboon 1 dying acutely with a rapidly developing hypotension and animals 5 and 6 surviving but exhibiting progressively decreasing pressures. Animal 2 died at 18 hours with the last measured parameters recorded at 8 hours. Blood glucose concentrations decreased whether the response was rapid, as with baboons 1 and 2, or prolonged, as with animals 5 and 6. The last recorded glucose values in

all animals varied between 21 and 55 mg%. Insulin values usually decreased and terminal hypoinsulinemia was seen in all baboons. Figure 1B shows that hematocrits were relatively stable except those of baboon 5, which decreased. Animals demonstrated maximal increases in temperature (T_R) 2 to 6 hours following initiation of Escherichia coli infusion. Arterial pH in each animal was relatively constant during the total observation period. Arginase concentrations increased sharply in animal 1 while SGPT values rose markedly in baboons 2 and 6, at 8 and 24 hours respectively (Figure 1C). Arterial potassium concentrations rose preterminally in all animals to values not exceeding 7 mEq/L, and sodium concentrations increased within 8 hours in baboons 1 and 2. Since the administered steroid MP is included in the adrenocortical assay procedure, concentrations are seen to be an order of magnitude higher in steroid-treated baboons compared with non-treated animals (Figure 1D). MP treatment did not alter survival rate in baboons receiving the lower dose of organisms and did not change any parameter measured in the untreated animals.

Figures 2A, 2B, 2C and 2D (Group B) show individual responses of baboons administered a mean dose of 1.9×10^{10} organisms/kg and one intramuscular dose of gentamicin (baboons 3 and 4), and one control baboon (animal 7) given saline only. Baboon 3 in this group was treated with MP. All three animals survived the 24-hour observation period. MSAP and blood glucose values were relatively constant for 24 hours although animal 4 had the lowest pressures and glucose values. Arterial insulin concentrations were variable, and baboon 4 had a markedly high insulin value of 140 μU/ml at 15 hours after Escherichia coli infusion (Figure 2A). Figure 2B shows that Hct, T_R and pH values were relatively constant in all animals, while Figure 3A shows that the SGPT level

was markedly elevated at 24 hours in baboon 4. Arginase and SGPT concentrations remained low in baboon 3 administered Escherichia coli, MP and gentamicin, as was also seen in the saline control. Sodium levels rose abruptly in both Escherichia coli-treated animals while potassium concentrations increased only in baboon 4 (3.5 to 6.0 mEq/L). Both Na^+ and K^+ levels were constant in the control baboon for the 24-hour period. Glucocorticoid levels were approximately ten times higher in the MP-treated animal (baboon 3) compared with baboons 4 and 7 not receiving the steroid (Figure 2D).

Figures 3A, 3B, 3C and 3D demonstrate individual responses of Group C baboons infused with a mean of 5.6×10^{10} organisms/kg, a dose approximately twice as great as that in Group A, animals 9, 10 and 11 receiving MP (45-60 mg/kg). All animals died within 11 hours after the initiation of organism infusion. Three baboons (8, 9 and 10) showed progressively developing hypotension while baboons 11 and 12 demonstrated a rapid onset of severe hypotension (Figure 3A). Blood glucose levels are seen to fall continuously, after an initial hyperglycemia, to lethal hypoglycemic values in four animals (7 to 46 mg%). In contrast, baboon 10 died in 7 hours with a marked hyperglycemia (151 mg%). Arterial insulin values decreased rapidly in this group in all but one baboon, and terminal hypoinsulinemia was observed in all animals (0-8 μU/ml). Baboon 9 exhibited a blood glucose value of 28 mg% and a 5.5 μU/ml insulin concentration at 4 hours following onset of Escherichia coli administration. Arterial pH values were relatively constant in these baboons except for terminal decreases in three animals and alkalosis in one animal. Hematocrit and temperature responses were variable although hemoconcentration was not observed in any animal (Figure 3B). Figure 3C illustrates marked increases in SGPT and arginase in baboon 10 and elevations of SGPT in animal

12. Arterial potassium concentrations rose in all animals to values not exceeding 6 mEq/L, while sodium concentrations were variable. Baboon 12 exhibited a decrease in plasma sodium concentration from 163 to 136 mEq/L in 11 hours. Figure 3D demonstrates that arterial glucocorticoid values were approximately ten times higher in steroid-treated animals.

Table II shows the effects of live Escherichia coli organisms on arterial blood lactate concentrations. Although lactate levels rose in all Escherichia coli-treated animals, in general increases are more marked in the baboons who died. Although there is an unexplained rise in lactate in the control animal at 5 hours, the subsequent values in this animal were relatively normal.

The average accumulated dose of Escherichia coli organisms administered prior to the first injection of MP was 2.0×10^9 organisms/kg in Groups A and C. Paired baboons, whether given Escherichia coli alone or Escherichia coli with steroid (MP), demonstrated no actual differences in physiologic, metabolic or morphologic findings. The pathologic findings in liver, kidney and adrenals are striking in all of the experimental animals. Lesions consisting of fibrin thrombi, edema and/or hemorrhage, and necrosis are present (7). The saline control showed no pathologic aberrations. All baboons except the control became markedly leukopenic, and similar degrees of leukopenia were observed from 2 to 15 hours in animals both with and without methylprednisolone. Differential cell evaluations were carried out and demonstrate a severe degree of neutropenia, including mature and immature cells, in all animals but the control. Small decreases in lymphocyte, monocyte and eosinophil concentrations were also noted from 2 to 15 hours after the onset of Escherichia coli infusion. The control baboon showed stable differential cell concentrations during the 24-hour observation period.

DISCUSSION

The present study was undertaken to evaluate the suitability of the unanesthetized baboon for studies relevant to human septic shock. Previous reports from this laboratory (6,17,19) have assayed hemodynamic, metabolic and morphologic responses of the anesthetized baboon to administrations of live Escherichia coli organisms or Escherichia coli endotoxin. The purpose of the present study was (a) to determine the responses of the unanesthetized instrumented baboon to 5-hour infusions of live Escherichia coli organisms at two dose ranges continuously observed during a 24-hour period or until death; and (b) to determine if treatment with pharmacological doses of the corticosteroid, methylprednisolone sodium succinate (MP), following infusions of Escherichia coli organisms is effective in improving the hemodynamic, metabolic, hematologic, morphologic and survival status of the animal. A 5-minute bolus injection of MP was given following the administration of 2.0×10^9 organisms/kg body weight, followed by infusions of MP at regular intervals in order to maintain its concentration at effective levels (half-life of MP, 3-4 hours). Administrations of MP were given beyond the 5-hour period in which the average infused organism quantity was 4.0×10^{10} organisms/kg, until 24 hours or death. No differences in physiologic, metabolic, hematologic or morphologic parameters were observed between treated and untreated animals, nor was survival time influenced by steroid administration. Since animals were carefully matched between treated and untreated groups, small improvements following steroid administration should have been detected. Since such was not the case, the reasons for the ineffectiveness of the steroid are in question.

Recent studies conducted by White and associates in this laboratory (38) have demonstrated clear protection against endotoxin shock by utilizing MP in dogs with a treatment regimen very similar to that used in the present study. White's group (38) showed that MP treatment prevented hypoglycemia, hemoconcentration and liver pathology, achieving an 80% survival rate with MP administration in LD_{100} endotoxin shock. The findings of Pitcairn (30) and Schumer (35) and associates in animals given Escherichia coli and in septic patients demonstrated significant protection against shock when MP was combined with antibiotic therapy.

Systemic hypotension would be expected to be lessened by the cardiovascular actions of MP, reported to include increased cardiac output by Sambhi and colleagues (33), increased inotropic support of the heart by Rao and Cavanagh (32), increased coronary blood flow by Hinshaw and associates (16), and increased regional blood flow by Vaughn (37) and Hinshaw (16) and co-workers. However, MP did not prevent systemic hypotension in the present study.

Hypoglycemia has been reported in canine live Escherichia coli-induced shock by Archer (1) and by Griffiths (11) and Groves (12) and their associates; in baboons receiving live Escherichia coli by Hinshaw and co-workers (17,19); and in human septic shock by Yeung (39) and Berk (2), Rackwitz (31) and their associates. Problems of glucose metabolism have been suggested in clinical shock cases by Cowley and others (9). The hypoglycemia of canine live Escherichia coli shock has been ascribed to impaired gluconeogenesis by Groves and others (12). Liver dysfunction and abnormal hepatic morphology were observed in the present study. MP administration would be expected to alleviate the hypoglycemia in baboons inasmuch as Berry (3) and Holtzman and colleagues (21) have found that corticosteroid administration stimulates

hepatic gluconeogenesis and Schuler and associates (34) have reported that MP supports carbohydrate metabolism in shocked nonhuman primates. MP utilized in the present study, however, did not intensify the degree of early hyperglycemia, nor did it alleviate the subsequently observed hypoglycemia.

Hypoinsulinemia, prominently demonstrated in the present study, was also uninfluenced by treatment with MP. Decreased insulin concentrations were observed in previous baboon shock studies by Hinshaw (17,19) and Cryer (10) and colleagues in lethal Escherichia coli septicemia in baboons. Clowes and co-authors (5) have observed hypoinsulinemia in patients with low cardiac outputs in septic shock, and hypoinsulinemia has been observed by Carey's group (4) in clinical hypovolemic shock. Hypoinsulinemia has been proposed to result from the combined effects of alpha adrenergic suppression of insulin release from the pancreas as reported by Cryer and associates (10) and diminished pancreatic blood flow in shock as shown by Lau and colleagues (24). Insulin resistance may be an added complication although its documentation in Escherichia coli shock is lacking.

Abnormal intravascular coagulation defects, exemplified in the present study by fibrin thrombi deposition in liver, kidney and adrenals, has also been reported in previous reports in the baboon administered live Escherichia coli by Coalson (6), Hinshaw (17,19), Holcroft (20) and Horwitz (22) and their associates, and in patients subjected to septic shock as reported by Corrigan and Jordan (8), Matsuda and Shimada (26) and McGovern (28). Latour and coworkers (24) have reported that glucocorticoids prevent generalized intravascular clotting, and it would be expected that MP would alleviate the degree of fibrin thrombi deposition in the present study. That such did not occur is contrasted with recent findings that although heparin administration

prevents the formation of fibrin thrombi in baboons subjected to Escherichia coli shock (19) and prevents disseminated intravascular coagulation in septic shock patients as reported by Corrigan and Jordan (8), increased survival rate is not realized nor is survival time extended.

Sibbald and associates (36) have recently observed variations in adrenocortical responsiveness during sepsis. Although cortisol levels in septic patients were markedly elevated in some instances (from control values of 8-18 μg/dl to 65 μg/dl), death occurred in each case. They propose that unrecognized adrenocortical insufficiency may be a critical factor in septic shock. Adrenal morphologic changes were striking in the present baboon study although cortisol concentrations were elevated above control in most instances. The effectiveness of these concentrations of cortisol and MP, however, may still not have been adequate in view of the findings of Sibbald and co-authors (36).

Since hemodynamic, metabolic, hematologic and morphologic defects were not prevented by methylprednisolone administration, it is not surprising that survival rate was not improved. However, steroid treatment alone in live Escherichia coli organism-induced shock in contrast to Escherichia coli endotoxin-induced shock may require other supportive measures in addition to MP, such as antibiotic administration.

SUMMARY

Recent studies from this laboratory have demonstrated that methylprednisolone sodium succinate (MP) increases survival rate in animals given LD_{100} Escherichia coli endotoxin. The purpose of this study was to determine the effects of MP on the baboon infused with live Escherichia coli organisms.

Awake animals were paired by infusing comparable intravenous doses of Escherichia coli during a 5-hour period. Baboons given MP received bolus injections of 30 mg/kg at 15 minutes after initiation of Escherichia coli infusion and 2-hour infusions of 15 mg/kg at 2-hour intervals until death or for a 24-hour period. Mortality rate was unaltered by MP. Six of 7 animals dying became progressively hypoglycemic while hypoinsulinemia occurred in all animals within 6 hours and was sustained until death. Systemic hypotension was observed, although pressures were variable. Potassium and lactate concentrations increased while pH remained relatively constant in most animals. SGPT and arginase concentrations rose in most baboons dying in 18 hours. Morphologic studies revealed the presence of fibrin thrombi in the liver, kidney and adrenal tissue in most animals. No significant differences in physiologic, metabolic, hematologic or morphologic parameters were observed between treated and untreated animals.

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TABLE I. SUMMARY OF DOSES OF LIVE ESCHERICHIA COLI ORGANISMS, METHYLPREDNISOLONE SODIUM SUCCINATE (MP), GENTAMICIN, OR SALINE AND SURVIVAL TIMES IN BABOONS

Group	Baboon No.	Sex	Weight (kg)	E. coli (org./kg)	Methylprednisolone (mg total)	Methylprednisolone (mg/kg)	Gentamicin (mg/kg)	Saline (ml total)	Saline (ml/kg)	Time of death (hr)
A	1	F	19.1	$3.0x10^{10}$				638	33	9
A	2*	F	12.6	$2.4x10^{10}$	737	58		486	39	18
A	5	F	12.6	$3.4x10^{10}$				900	71	Survivor
A	6	F	15.3	$2.6x10^{10}$	1610	105		1040	68	Survivor
B	3	F	16.2	$1.7x10^{10}$	1884	116	4.4	1520	94	Survivor
B	4	F	14.3	$2.0x10^{10}$			4.4	1500	105	Survivor
Control	7	M	15.5					960	62	Survivor
C	8	F	9.6	$5.2x10^{10}$				340	35	7
C	9	F	14.2	$5.1x10^{10}$	639	45		248	17	4
C	10	F	13.7	$6.8x10^{10}$	823	60		380	28	7
C	11	F	14.1	$5.6x10^{10}$	847	60		390	28	8
C	12	F	17.6	$5.2x10^{10}$				420	24	11

TABLE II. EFFECTS OF INFUSED LIVE ESCHERICHIA COLI ORGANISMS ON ARTERIAL BLOOD LACTATE CONCENTRATIONS IN BABOONS

Group	Baboon No.	Time during shock, hrs. Control	2	4	5	6	7	8	10	11	15	20	24
A	1	29.8	36.3	87.4		97.6		$113.0^{d,9*}$					
A	2*	14.9	62.7	78.2		54.4		$67.6^{d,18}$					
A	5	30.9	20.6		48.7				57.7		49.5		55.5
A	6	38.1	34.2		38.6				56.6		52.2	68.5	55.4
B	3	16.3	83.4		37.4				54.8		33.8	35.2	38.6
B	4	15.1	30.3		36.4				36.4		36.5	43.5	38.7
Control	7	†	11.9		47.0				9.7		7.4	6.4	8.2
C	8	5.0	22.2		40.4		$42.0^{d,7}$						
C	9	9.1	37.6	$136.0^{d,4}$									
C	10	11.6	47.9		80.6		$223.0^{d,7}$						
C	11	20.8	30.7		50.6			$97.6^{d,8}$					
C	12	12.2	22.5		25.1				26.0	$48.4^{d,11}$			

*time of death
†observed for 8 hours
§insufficient sample

Figures 1A, 1B, 1C and 1D (Group A):

Effects of methylprednisolone sodium succinate (MP) administration on baboons subjected to five-hour infusions of live Escherichia coli organisms (mean dose, 2.9×10^9 organisms/kg body weight).

*MP, 30 mg/kg, intravenously administered, 15 minutes following onset of Escherichia coli infusion.

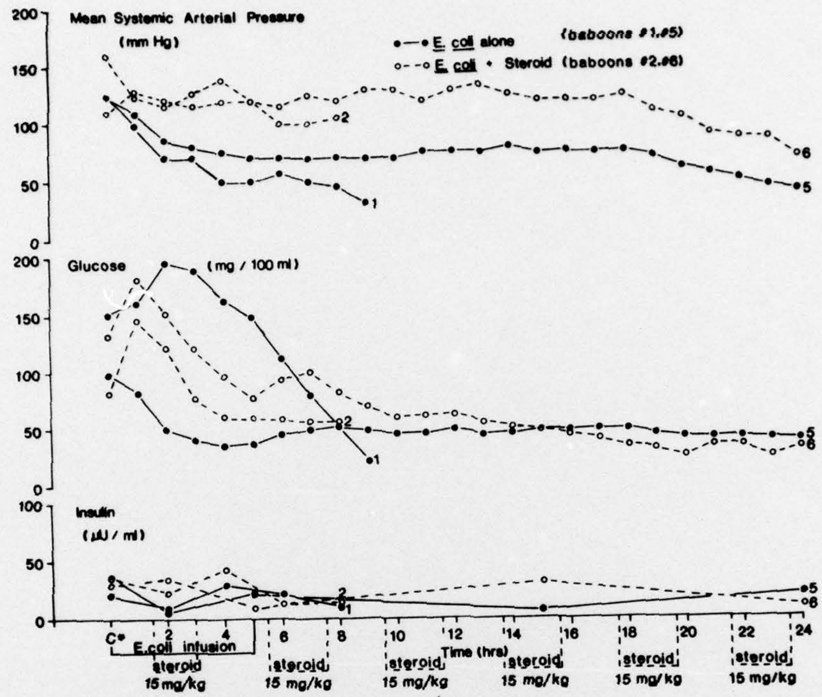

FIGURE 1A

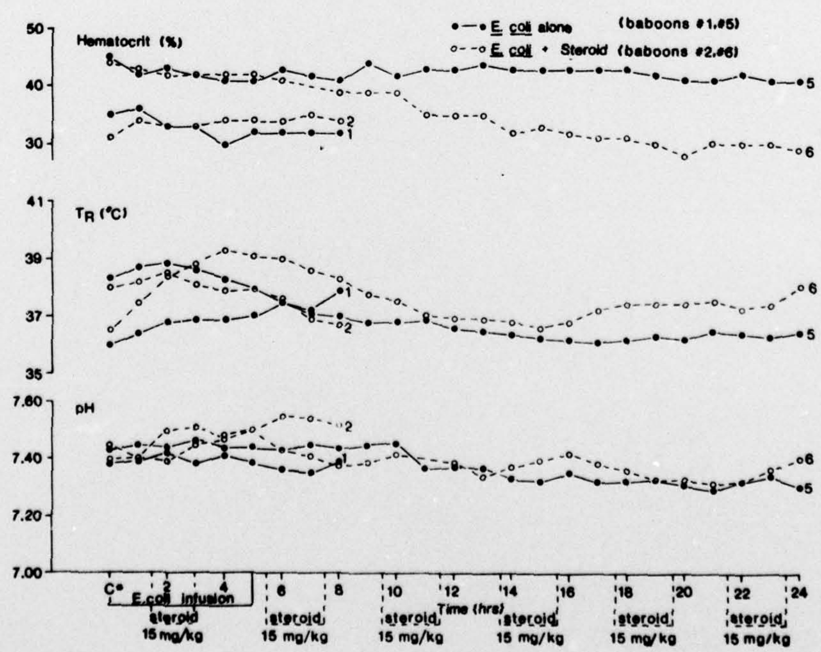

FIGURE 1B

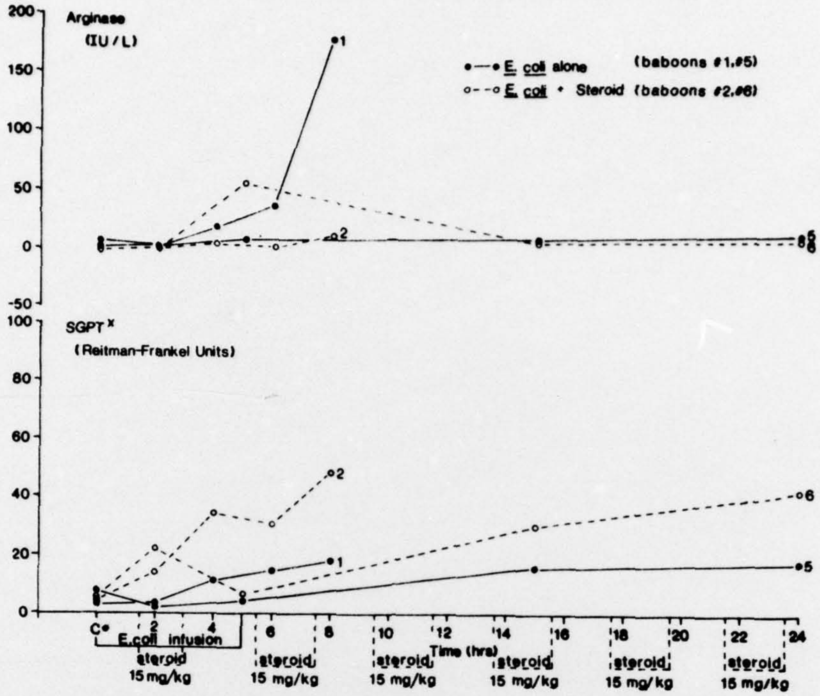

FIGURE 1C

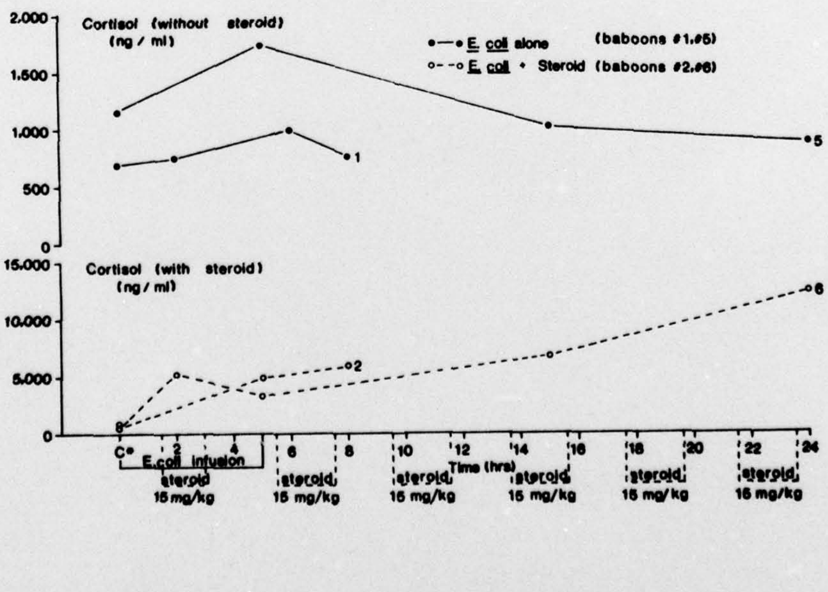

FIGURE 1D

Figures 2A, 2B, 2C and 2D (Group B):

Effects of methylprednisolone sodium succinate (MP) administration on baboons subjected to five-hour infusions of live Escherichia coli organisms (mean dose, 1.9×10^{10} organisms/kg body weight) and given gentamicin at 6.5 hours. One control animal received saline only.

*MP, 30 mg/kg intravenously administered, 15 minutes following onset of Escherichia coli infusion.

**Gentamicin, 4.4 mg/kg, intravenously administered, 1.5 hours following completion of Escherichia coli infusion.

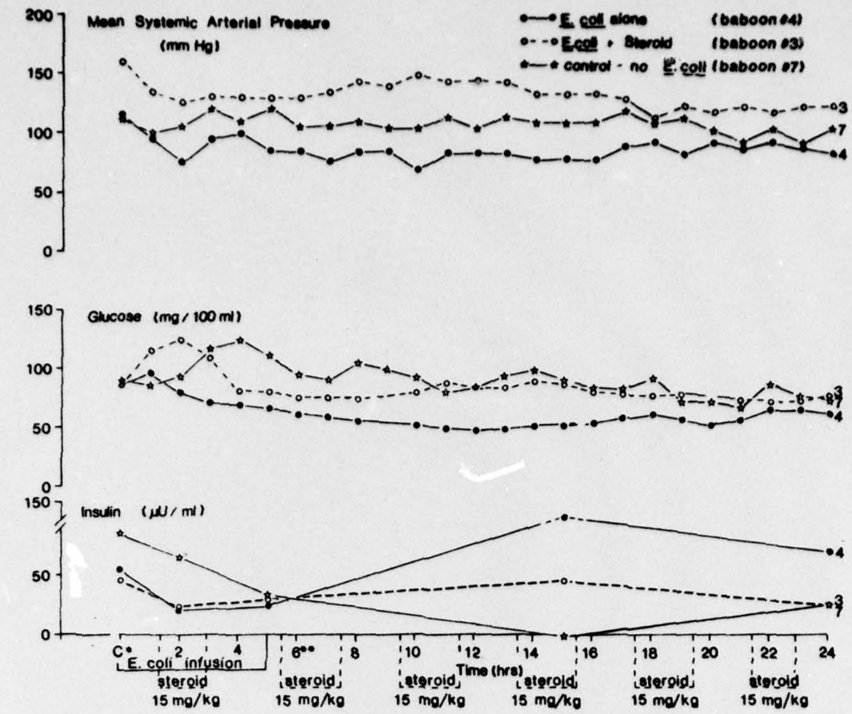

FIGURE 2A

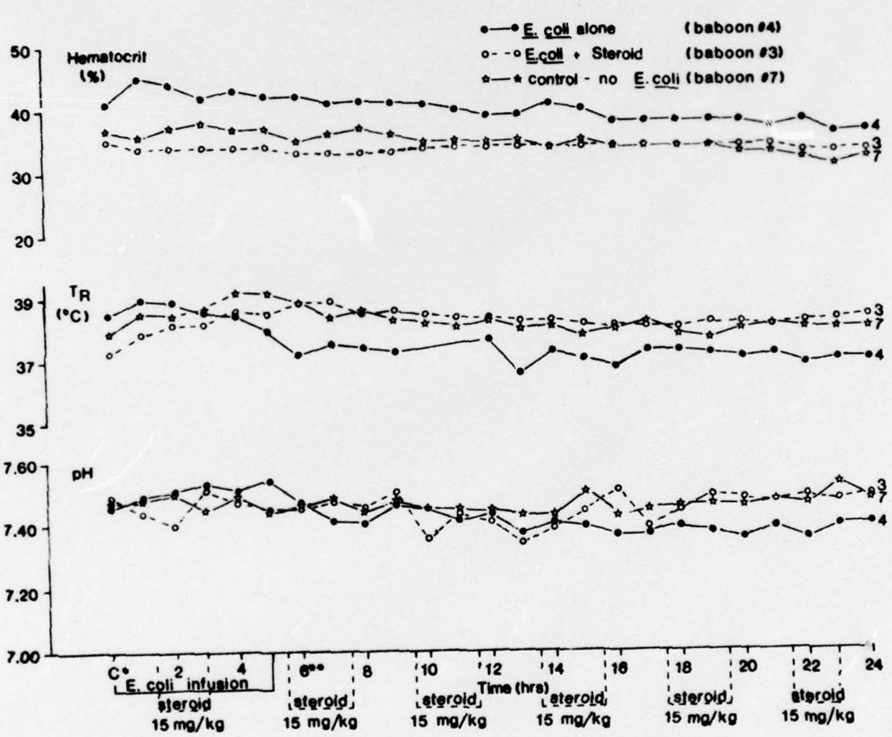

FIGURE 2B

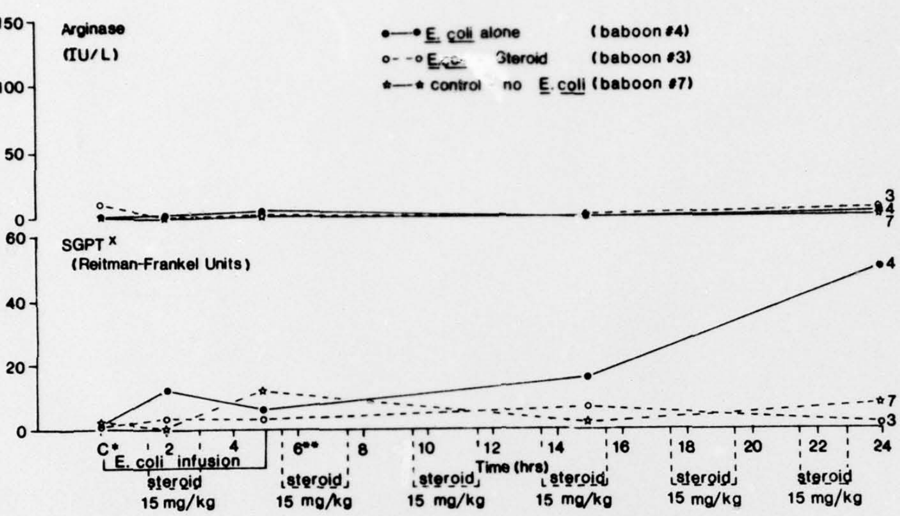

FIGURE 2C

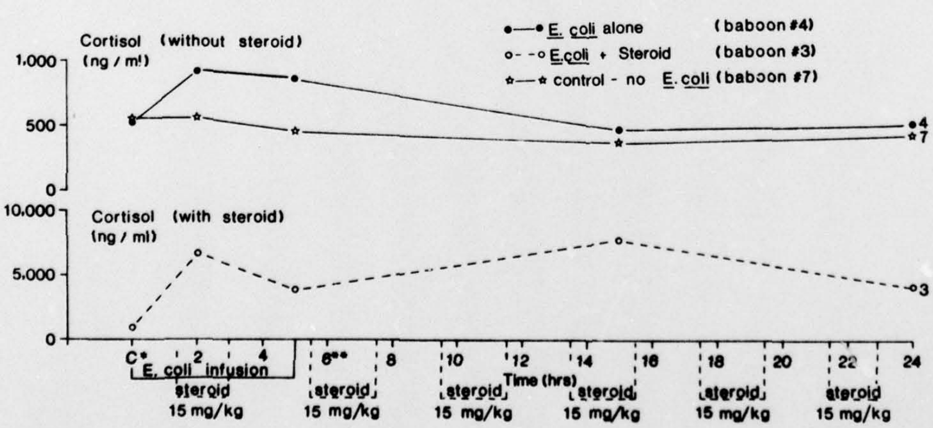

FIGURE 2D

Figures 3A, 3B, 3C and 3D (Group C):

Effects of methylprednisolone sodium succinate (MP) administration on baboons subjected to five-hour infusions of live Escherichia coli organisms (mean dose, 5.6×10^{10} organisms/kg body weight).

*MP, 30 mg/kg, intravenously administered, 15 minutes following onset of Escherichia coli infusion.

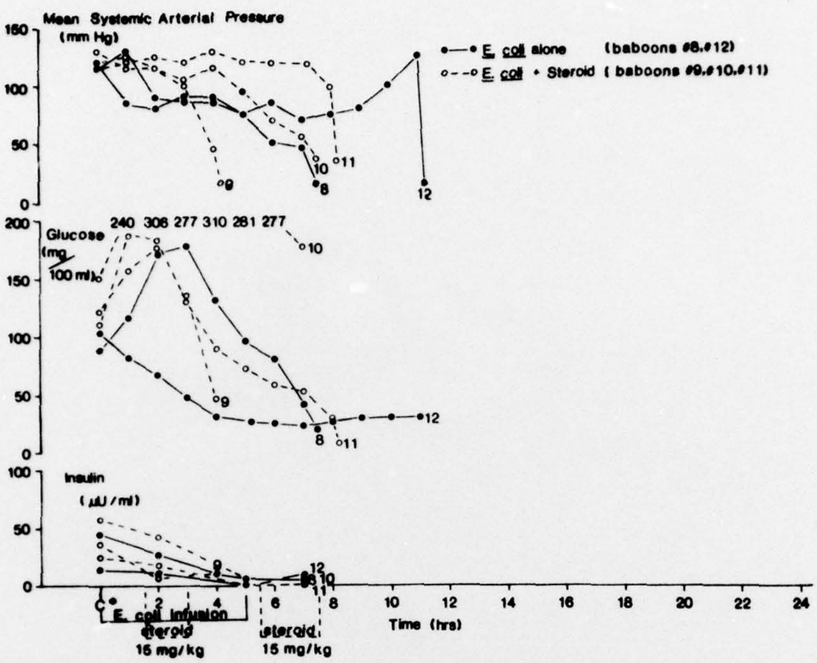

FIGURE 3A

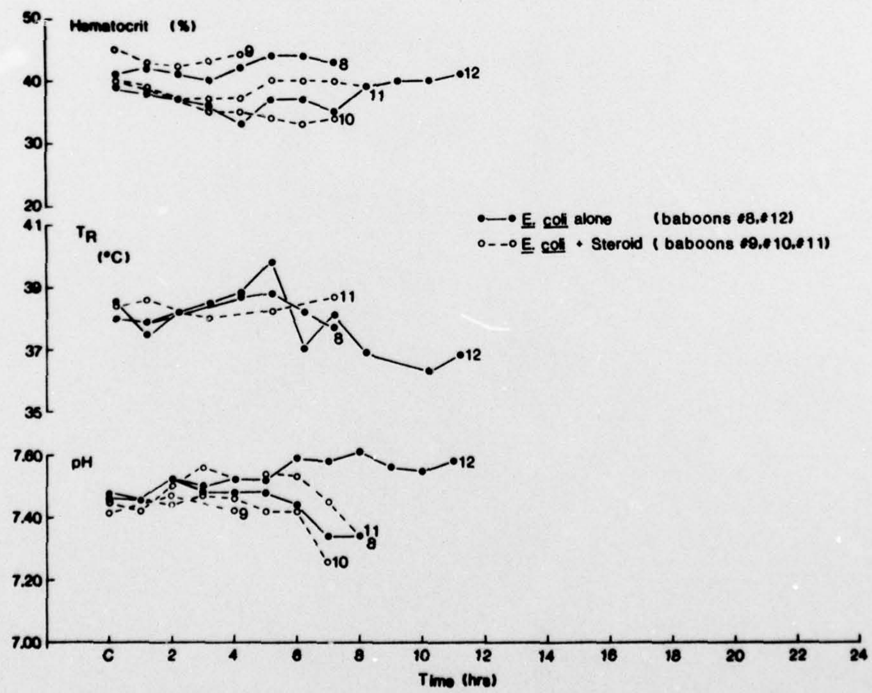

FIGURE 3B

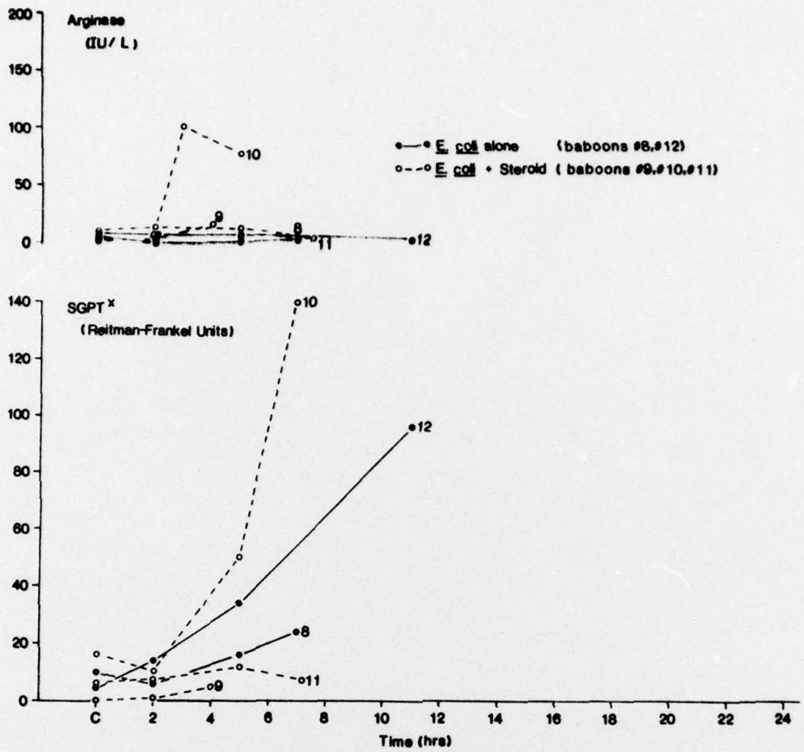

FIGURE 3C

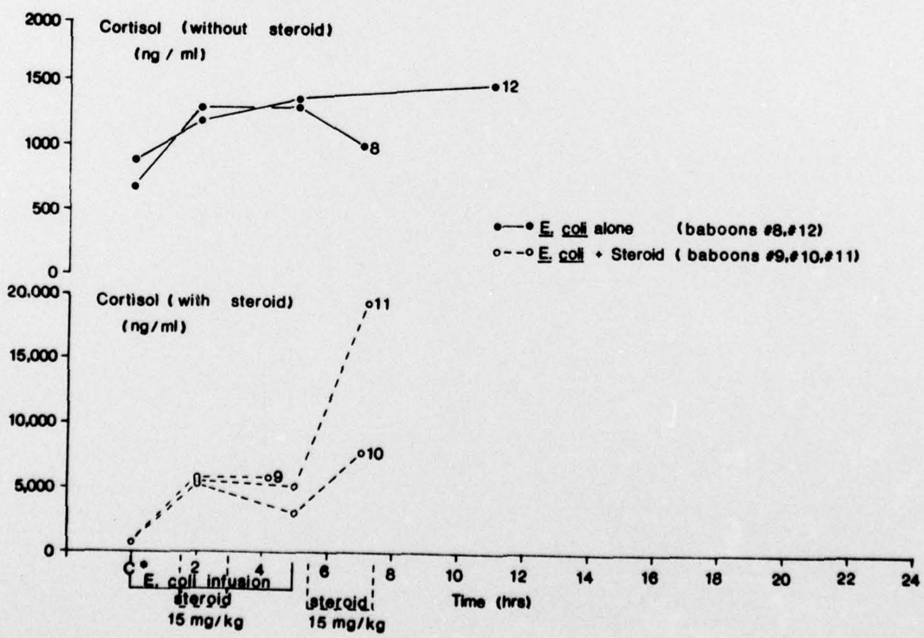

FIGURE 3D

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Recent studies from this laboratory have demonstrated that methylprednisolone sodium succinate (MP) increases survival rate in animals given LD_{100} Escherichia coli endotoxin. The purpose of this study was to determine the effects of MP on the baboon infused with live Escherichia coli organisms. Awake animals were paired by infusing comparable intravenous doses of Escherichia coli during a 5-hour period. Baboons given MP received bolus injections of 30 mg/kg at 15 minutes after ~~(cont.)~~

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initiation of Escherichia coli infusion and 2-hour infusions of 15 mg/kg at 2-hour intervals until death or for a 24-hour period. Mortality rate was unaltered by MP. Six of 7 animals dying became progressively hypoglycemic while hypoinsulinemia occurred in all animals within 6 hours and was sustained until death. Systemic hypotension was observed, although pressures were variable. Potassium and lactate concentrations increased while pH remained relatively constant in most animals. SGPT and arginase concentrations rose in most baboons dying in 18 hours. Morphologic studies revealed the presence of fibrin thrombi in the liver, kidney and adrenal tissue in most animals. No significant differences in physiologic, metabolic, hematologic or morphologic parameters were observed between treated and untreated animals.

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